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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,997	09/18/2003	Carol Carter	FUNC-0017-CO1	6642

80308 7590 05/11/2009

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EXAMINER	
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ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
05/11/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/666,997	CARTER ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-91 and 93-134* is/are pending in the application.

4a) Of the above claim(s) *59-91 and 95-131* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *93,94 and 132-134* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the remark filed 25 February 2009. Claims 1-58 and 92 have been cancelled. Claims 59-91 and 93-134 are pending. Claims 59-91 and 95-131 are drawn to a nonelected subject matter and hence are withdrawn from further consideration pursuant to 37 CFR 1.142(b). Claims 93, 94 and 132-134 are currently examined.

Applicant's traversal of the restriction is noted and not further considered as the restriction was deemed to be proper and made FINAL in the previous Office Action mailed on 26 February 2007.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 93, 94 and 132-134 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement is **maintained** for reasons of record.

Claims 93, 94 and 132-134 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a

way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112, first paragraph, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

Claims 93, 94 and 132-134 are directed to a method of inhibiting human immunodeficiency virus (HIV) particle generation in cells comprising administering a peptide comprising a PTAP motif that inhibits binding between tumor susceptibility gene (Tsg101) protein and HIV Gag polypeptide.

The breadth of the claims encompass inhibiting HIV particle formation in any kinds of cells, including *in vivo* and *in vitro*, suspected to be infected by any strain or subtype of HIV by inhibiting the binding of any form of Tsg101 and the Gag protein of any strain or quasi-species of HIV. With the exception of claim 132 limiting the peptide to comprise SEQ ID NO:4, the claimed peptide is a genus of variants with different length from the four amino acid peptide, PTAP, to any large protein containing the four amino acids, PTAP. Further, claims 93, 94 and 132 do not claim whether the anti-HIV peptide acts on a target that is conserved among all hosts.

The disclosure does not provide any working embodiments that meet the claimed limitations. While there is one cell culture example (page 37-41) identifying the binding regions of Gag p6 late domain and Tsg101 and mutating by deletion of the binding region in either Tsg101 or Gag protein to observe the effect on particle release by HIV vector-transfected COS cells, there is no *in vitro* or *in vivo* working example that shows the effectiveness of any PTAP-containing peptides in inhibiting particle formation. Furthermore, the Gag p6 late domain does not represent the entire genus of the PTAP- containing peptides. The Gag protein is neither conserved between the two HIV serotypes, HIV-1 and HIV-2, nor among the abundant strains or quasi-species of HIV. Therefore, the peptide binding affinity/avidity is questionable.

The specification provides no guidance regarding practice of the claimed method. The amount of direction is limited to one cell culture assay identifying the binding regions in HIV Gag p6 late domain and Tsgl01 (Example 1) and the amount of released mature HIV particles as a result of mutated binding regions in Tsg101 and HIV Gag p6 late domain (Example 2). The disclosed example is not even a test of a peptide inhibitor for the interaction between Tsg101 and Gag. There is no evidence that shows any correlation with in vivo efficacy to confirm the Applicant's theory deduced from the cell culture results. There is no teaching about the therapeutic properties such as the binding specificity, selectivity and affinity, oral bioavailability, cellular uptake, toxicity, lethal dose, and side effects for administering a PTAP-containing peptide into a cell inside a body. There is not even a test to determine the efficacy and resistance of the claimed genus of Tsg101 binding inhibitors. Therefore, the disclosure does not relate to inhibiting HIV particle formation in cells *in vitro* or *in vivo*.

There is a high level of uncertainty and unpredictability in the art. The development of suitable HIV-1 inhibitors has been an arduous and empirical process, often ending in failure (Hendrix, 2000, first and last paragraph; Gait, 1995). This is due to a number of factors: (1) failure to understand the molecular determinants modulating many viral protein and host cell factor interactions; (2) failure of in vitro tissue culture studies and in vivo

animal models to adequately predict clinical efficacy; (3) failure of many compounds to have acceptable pharmacological profiles despite initial favorable in vitro and in vivo activities; and (4) failure of related structural analogs to function in the desired manner, which provides further evidence of the specificity of these molecular interactions. The challenges of developing efficacious anti-HIV agents are best summarized by Gait and Karn (1995) who state in the Conclusions (p.37): There can be few tasks in biotechnology that are more challenging than designing antiviral drugs. All of the protease inhibitors that have entered into clinical trials are potent inhibitors of HIV-1 replication in cell culture, and exhibit remarkable selectivity for the viral enzyme. Unfortunately, early protease inhibitors tended to suffer from problems of short serum half-life, poor availability and rapid clearance. As these pharmacokinetic problems have been addressed and solved, new difficulties have emerged from the resultant clinical experience, such as sequestration of the drug by serum proteins, drug resistance and uneven distribution throughout the body. Since these types of problems are unpredictable, it remains necessary to take into account the pharmacological parameters in any drug development programme at the earliest possible stage.

The art of HIV particle inhibitors is highly unpredictable because the effect of such a compound appears to change due to pharmacokinetic

variation, fluctuating adherence, the emergence of drug resistant mutations and/or other factors. Inadequate drug concentrations can result from a number of factors including non-adherence, pharmacokinetics, and lack of drug potency. In addition, anatomical sanctuary sites may exist where drug concentrations do not achieve adequate levels despite apparent therapeutic serum drug concentrations. HIV replication can occur in such settings, and the selective pressure of antiretroviral therapy leads to the emergence of HIV harboring drug-resistant mutations. Thus, a key element in future drug design strategies is to understand how drug resistance mutations affect the interaction of the drug with its target, and to then develop compounds with the adaptability to inhibit these variants along with wild-type HIV (Yin, 2006). Therefore, efforts to develop effective treatments must overcome the complex evolutionary dynamics in HIV-infected individuals and within affected populations.

In the instant case, a Tsg101-Gag binding inhibitor as an AIDS drug is not considered routine in the art. The disclosure fails to address any of the aforementioned caveats in the development of an antiviral agent. Without sufficient guidance to the safety, bioavailability, plasma concentration, and antiviral effect, the experimentation left to those skilled in the art is undue or unreasonable under the circumstances.

For the reasons discussed above, it would require undue and unpredictable experimentation for one skilled in the art to use the claimed method.

Response to Arguments

Applicant's arguments filed 25 February 2009 have been fully considered but they are not persuasive. First, Applicants contend that the Examiner has characterized the claims as embracing the use of antibodies that bind to Tsg101 on the surface of the HIV infected cells. It is respectfully clarified that this is never the Examiner's interpretation of the rejected claims. After Applicants' amendment filed on 29 May 2009 changing the claim limitations of claims 93 and 94 from administering "a compound" to administering "a peptide comprising a PTAP motif," the enablement rejection has been maintained accordingly with rationale and reasons based upon the method of inhibiting HIV particle generation in cells comprising administering a peptide comprising a PTAP motif. Applicants argue that the Office Action mailed on 8 August 2007 expressly states again that the breadth of the claims embraces the used of antibodies on page 3. Examiner respectfully disagrees with Applicants' statement that "the Examiner has not otherwise construed or characterized the claims" on page 20 of the remark filed on 25 February 2009. Applicants seem to have

misread the Office Action. It is respectfully clarified that the Office Action mailed on 8 August 2007 contains a summary of the previous enablement rejection as presented in the previous Office Action mailed on 05 June 2006. In other words, the sentence stating that "the claims... encompass siRNA, aptamers, ribozymes, antibodies, small molecule inhibitors, and Gag homologs" is lifted out of the section under the heading: "Examiner's rejection in the Action mailed on 05 June 2006 is as follows..." See Office Action mailed 8 August 2007, page 3, lines 3, summarizing the Examiner's enablement rejection of the claims prior to the claim amendment on 29 May 2007. Furthermore, Examiner clearly set forth the updated claim interpretation as the following:

> "The breadth of the claims encompass inhibiting HIV particle formation in any kinds of cells, including in vivo and in vitro, suspected to be infected by any strain or subtype of HIV by inhibiting the binding of any form of Tsg101 and the Gag protein of any strain or quasi-species of HIV. With the exception of claim 132 limiting the peptide to comprise SEQ ID NO:4, the claimed peptide can be from a PTAP peptide to any protein containing the four amino acids, PTAP. Further, claims 93, 94 and 132 do not claim whether the anti-HIV peptide acts on a target that is

conserved among all hosts." See page 4 of the Office Action mailed on 25 November 2008.

The most recently mailed Office Action never mentions antibodies. Therefore, the record has been very clear that Examiner has been characterizing the claims as amended.

Second, Applicants assert that the outstanding Action acknowledges that Applicants' disclosure as originally filed DOES enable: "a method for identifying all PTAP-containing peptides that are effective at inhibiting the binding between Tsg 101 and the HIV Gag protein and thereby blocking the HIV particle generation in the virus life cycle." However, a method of identifying HIV Gag binding region peptides is a long way from the claimed method of inhibiting HIV particle generation in cells. The instant application merely discloses the identification of the binding region between HIV Gag and Tsg101 and effect of particle release in vitro, which cannot be extrapolated to a method of identifying peptides preventing the PTAP region of Gag protein from interacting with Tsg101, which is not even representative or predictive of the effectiveness of any PTAP-containing peptides inhibiting HIV particle formation in any cells, especially cells inside a patient. Applicants have not provided any evidence that validates the theory that a PTAP-containing peptide of any length is an effective inhibitor of Gag-Tsg101 binding and reduces particle formation. The disclosed

example is not even a test of a peptide inhibitor for the interaction between Tsg101 and Gag. There is no evidence that shows any correlation with in vivo efficacy to confirm the Applicant's theory deduced from the cell culture results. There is no teaching about the therapeutic properties such as the binding specificity, selectivity and affinity, oral bioavailability, cellular uptake, toxicity, lethal dose, and side effects for administering a PTAP-containing peptide into a cell inside a body. There is not even a test to determine the efficacy and resistance of the claimed genus of Tsg101 inhibitors. Therefore, the disclosure does not correlate with inhibiting HIV particle formation in cells *in vitro* or *in vivo*.

Third, Applicants argue that the examined claims do not recite treating HIV. However, the claims are directed to administering a PTAP peptide to cells, which encompass both culture dish cells and human body cells. The latter reads on administering a PTAP peptide to a living host cell, which would be a cell inside a human since humans are the natural hosts of HIV infection. The claims do not limit "the cell" to be the in vitro cells used in the assay for identifying PTAP peptides that inhibit binding between Tsg101 and HIV Gag. Therefore, the claim limitation "administering to cells" reads on administering to cells in a human. Applicants' assertion "AIDS is not HIV infection – the two are not the same" is not supported by any reasons. A method of inhibiting HIV infection *of cells in a living body* is the same as a

therapy for AIDS, the symptomatic manifestation of the human cell infection by HIV. Therefore, the art recognized problems in the development of a HIV/AIDS inhibitor - drug resistant mutations, non-adherence, poor pharmacokinetics - have relevance to the examined claims and raise the issue of unpredictability when considering the enablement of the disclosure as filed.

Fourth, Applicants state that they are not targeting HIV, followed by the explanation that, by interfering with binding between the virus and a (host cell) surface molecule, a method of inhibiting particle formation (the binding is required for particle formation) without putting selection pressure on the virus is provided. Applicants' arguments are contradicting. It is unclear why Applicants think that a method of inhibiting/targeting HIV Gag – Tsg101 binding is not targeting HIV.

Fifth, Applicants' argument regarding the identical specification in the U.S. Patent 7,494,767 is not germane to the rejection at issue because each case is evaluated on its own merits. The claimed invention differs from the patented invention. The fact pattern of the instant application is different from that of the U.S. Patent 7,494,767. Every case is evaluated on its own merits.

Sixth, Applicants' argument regarding the relevance of the antibody inhibition data is not convincing. An antibody is completely different from the product, a peptide comprising PTAP, used in the claimed invention.

Finally, Applicants' statement, Examiner's rejection is based upon insufficient evidence to demonstrate that interfering in the binding between Tsg 101 and HIV actually results in reduced particle formation, mischaracterizes Examiner's rationale for the enablement rejection. Applicants' argument "whether viewed in vivo or in vitro, if you concede that the peptides of the invention inhibit particle formation, there is abundant evidence of record that clearly demonstrates that notwithstanding prior art issues, even IF demonstration of anti- AIDS efficacy was required, the peptides claimed will exhibit that efficacy" further misconstrues the rejection. This is not the Examiner's position. The Office has never conceded that the peptides of the invention inhibit particle formation. Rather, Examiner acknowledges the disclosure of the method to identify HIV particle inhibitor peptides, which cannot be extrapolated to a method of inhibiting HIV particle generation by administering PTAP-containing peptides to cells for reasons set forth above and in the previous Office Action mailed on 25 November 2008 on pages 3-7.

Examiner's rejection is based on the lack of any demonstration of both *in vitro* and *in vivo* particle inhibition activity of any PTAP-containing peptide,

the high level of unpredictability in the *in vitro–in vivo* correlation for HIV inhibition, the heterogeneity of the HIV affecting the inhibitor binding affinity and efficacy. Applicants have not addressed any of these issues in their responses. Applicants have not responded to the fact that the claim limitation "cells" reads on both *in vitro* cell culture and living cells in a human body, which means HIV inhibition therapy, hence Examiner presented the issues of satisfying the therapeutic properties such as the cellular uptake, binding specificity/selectivity/affinity, oral bioavailability, toxicity, lethal dose, and side effects for administering a PTAP-containing peptide into a cell inside a body, as well as the challenges for the development of a HIV inhibitor that are well known to one skilled in the art.

For all of the above reasons, the rejection of claims 93, 94 and 132-134 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement is maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action

and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648
6 May 2009

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643